IN THE SPECIFICATION

Please amend the fourth full paragraph on page 2, lines 16-22 as follows:

Figure 3: Sequence of Ar6pAE2fF from left and right ends of viral DNA. Regions of Ar6pAE2fF confirmed by DNA sequencing (SEQ ID NO: 3). Panel A. Regions in first 1802 nucleotides are ITR (nucleotides 1-103), poly-adenylation signal (nucleotides 116-261), human E2F-1 promoter (nucleotides 283-555), E1a gene (nucleotides 574-1647) and a portion of the E1b gene (nucleotides 1648-1802). Panel B. Regions in the last 531 nucleotides (SEQ ID NO:4) are the PacI restriction site (nucleotides 33967-33974) (underlined), the packaging signal (nucleotides 34020-34217 and the ITR (34310-34412).

Please amend the fifth full paragraph on page 2, lines 23-25 as follows:

Figure 4: Sequence of Ar6F from left end of viral DNA. The first 660 nucleotides at the left end of Ar6F (SEQ ID NO: 5). The ITR (nucleotides 1-103), a multiple cloning site (MCS) (nucleotides 104-134) and a portion of the E1a gene (nucleotides 135-660) are shown.

Please amend the first full paragraph on page 3, lines 1-3 as follows:

Figure 5: Sequence of Ar6pAF from left end of viral DNA. The first 660 nucleotides at the left end of Ar6paF (SEQ ID NO: 6). The ITR (nucleotides 1-103), the SV40 early polyA signal (nucleotides 104-134) and a portion of the E1a gene (nucleotides 298-660) are shown.

Please amend the second full paragraph on page 8, as follows:

A termination signal sequence within the meaning of the invention may be any genetic element that causes RNA polymerase to terminate transcription. A polyadenylation signal sequence is a recognition region necessary for endonuclease cleavage of an RNA transcript that is

followed by the polyadenylation consensus sequence AATAAA (nucleotides 72-76 of SEQ ID NO: 1). A polyadenylation signal sequence provides a "polyA site", i.e. a site on a RNA transcript to which adenine residues will be added by post-transcriptional polyadenylation. Polyadenylation signal sequences are useful insulating sequences for transcription units within eukaryotes and eukaryotic viruses. Generally, the polyadenylation signal sequence includes a core poly(A) signal which consists of two recognition elements flanking a cleavage-polyadenylation site (Figure 1). Typically, an almost invariant AAUAAA hexamer (transcribed RNA of nucleotides 72-76 of SEQ ID NO: 1) lies 20 to 50 nucleotides upstream of a more variable element rich in U or GU residues. Cleavage between these two elements is usually on the 3' side of an A residue and in vitro, is mediated by a large, multicomponent protein complex. The complex includes the cleavage and polyadenylation specific factor (CPSF), which binds the AAUAAA motif; the cleavage stimulation factor (CstF), which binds the downstream U-rich element; and two additional cleavage factors (CF I and CF II) that are less well characterized. Also, the poly(A) polymerase must be present in most cases for the cleavage step as well. The choice of a suitable polyadenylation signal sequence will consider the strength of the polyadenylation signal sequence, as completion of polyadenylation process correlates with poly(A) site strength (Chao et al., Molecular and Cellular Biology, August 1999, pp5588-5600). For example, the strong SV40 late poly(A) site is committed to cleavage more rapidly than the weaker SV40 early poly(A) site. The person skilled in the art will consider to choose a stronger polyadenylation signal sequence if a more substantive reduction of nonspecific transcription is required in a particular vector construct.

Please amend the third full paragraph on page 9 as follows:

An analysis of the characteristics of the nucleotide elements around the adenoviral (Ad5) E1a region indicates that an element containing enhancer like properties lies between -141 and -305 relative to the Ela cap site at +1 (Figure 2). This enhancer element is located very close to a sequence required in cis for packaging of viral DNA. Deletion of the enhancer element reduces both the rate of transcription and steady-state levels of E1a mRNAs in virus-infected cells. The E1a enhancer contains an 11 bp repeat element, which is a critical component of the modulatory sequence (5'-AGGAAGTGACA-3; nucleotides 199-209 of SEQ ID NO: 4) ~~(SEQ ID NO:7)~~. A 2-3-fold reduction of E1a expression is observed when one copy of the repeat sequence is removed, whereas expression drops 15 to 20 times when both copies are removed (Hearing and Shenk, Cell vol. 33, pp.695-303, July 1983). However, it was found that a deleted mutant can still direct the synthesis of E1a-specific mRNAs, even though it lacks the entire region from -393 to +10 relative to the E1a cap site containing the enhancer and promoters elements. It is not clear which sequences are responsible for this transcription. Accordingly, in the context of adenoviral vectors, the interfering genetic element may be located within the 5'ITR, which is a region necessary for replication of the adenovirus.

Please amend the third full paragraph beginning on page 17 continuing onto page 18 as follows:

Two adenovirus backbones that were expected to minimize nonspecific activation of the E1a gene were developed. The Ar6F adenoviral vector contains the left side ITR directly linked to the E1a coding region, with the intervening nucleotides deleted (nucleotides 104-551 in the Ad5 sequence, GenBank accession number M73260) and replaced with a multiple cloning site (FIG. 4; SEQ IDNO: 8). The Ar6pAF adenoviral vector is identical to Ar6F except that it

contains the 145 nucleotide SV-40 early poly(A) signal inserted between the left ITR and the E1a coding region (FIG. 5; SEQ ID NO: 9). In both of these vectors, the packaging signal normally present near the left ITR was moved to the right ITR (FIG. 3, panel B; SEQ ID NO: 7). This was performed by replacing the right ITR with the reverse complementary sequence of the first 392 bp of Ad5, which contains the left ITR and the packaging signal. Finally, to generate the adenoviral vector Ar6pAE2fF, the tumor selective promoter E2F-1 was inserted between the SV-40 early poly(A) signal and the E1a coding region present in Ar6pAF (FIG. 3, panel A; SEQ ID NO:6).

Please amend the first full paragraph on page 18 as follows:

The first 1802 nucleotides of the Ar6pAE2fF adenoviral vector, including the ITR, poly(A), E2F-1 promoter and the E1a gene was confirmed by DNA sequencing (SEQ ID NO:3). In addition, the last 531 nucleotides at the right end of the vector, containing the packaging signal and right ITR was confirmed by sequencing (FIG. 3; SEQ ID NO:4).